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Nucleophilicity towards a Saturated Carbon Atom: Rate Constants for the Aminolysis of Methyl 4-Nitrobenzenesulfonate in Aqueous Solution. A Comparison of the *n* and N_+ Parameters for Amine Nucleophilicity

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Second-order rate constants (k_{Nu}) have been measured in aqueous solution (I = 0.1 mol dm^{-3}, 25 °C) for the S_N2 reactions of methyl 4-nitrobenzenesulfonate with ammonia, 41 primary amines, 20 secondary amines, 29 tertiary amines and 7 anionic nucleophiles. For the aminolysis reactions, Brønsted-type correlations of nucleophilicity with basicity require the classification of all amines in terms of strictly defined structural classes with β_{nuc} in the range 0.15–0.39. Swain–Scott plots indicate that simple amines, water and other light-atom nucleophiles (hydroxide, azide and cyanide anions) are five times more reactive than heavy-atom nucleophiles (thiosulfate, thiocyanate, iodide and bromide ions). For amine nucleophiles there is a close linear correlation (of slope 0.44, and including both primary and secondary amines) between log k_{Nu} for the aminolysis of methyl 4-nitrobenzenesulfonate and log k_{Nu} for amine addition to the 1-methyl-4-vinylpyridinium cation. This correlation demonstrates a close linear relationship between the Swain–Scott *n* parameter and Ritchie's N_+ parameter for amine nucleophiles in aqueous solution ($N_+ = 2.1n - 4.3$).

Nucleophilicity is a fundamental concept for the description of a broad range of chemical reactions in solution. However, a broadly applicable quantitative measurement of nucleophilicity remains elusive, despite this concept's widespread utility and obvious close relationship to basicity. Several parameters to describe nucleophilic character have been defined and evaluated for a wide range of nucleophiles reacting with either sp^2- or sp^3-hybridized carbon electrophiles. Ritchie's N_+ parameter[1] for attack upon an sp^2 carbon atom has proved to have wide applicability for nucleophilic attack upon unsaturated carbon electrophiles. An analogous parameter *n* was defined by Swain and Scott[2] for nucleophilic attack upon saturated carbon atoms in aqueous solution, and was further extended by Pearson and coworkers[3] for reactions in methanolic solution. Each of these parameters is defined in an analogous empirical fashion in terms of relative second-order rate constants for nucleophilic attack upon a common electrophilic substrate (originally triarylmethyl cations in aqueous solution[1] for N_+ and methyl bromide in aqueous solution[2] for *n*). In each case, the reaction of the appropriate electrophile with water was defined as the standard reference reaction for which $N_+ = 0$ or $n = 0$.

Despite the similarity in the empirical basis for the definition of each of these two parameters, there appears to have been little serious attempt to investigate in a systematic quantitative manner whether a relationship between N_+ and *n* may exist. The exploration of the relationship between these two parameters is not a simple matter when one considers the broad range of factors which have been found to influence nucleophilicity; for instance, Bunnett[4] listed 17 factors which he considered to play a role in the determination of nucleophilic reactivity. Even a simplified list limited to basicity, electrical charge, solvation, steric phenomena and polarizability is rather daunting when one realizes that these factors are often interrelated, and in some cases are difficult to quantify in any general way for solution reactions.

Amines represent by far the largest class of nucleophiles in which one can systematically vary reactivity through structural change, while at the same time maintaining a constant nucleophilic centre. In this series of nucleophiles, variations in electrical charge and polarizability are essentially eliminated, and quantitative measurements of the basicity of an enormous number of amines are available in aqueous solution. Although solvation phenomena and steric effects are not readily quantified, they are expected to vary systematically with structural modifications in the amine nucleophile. Amine nucleophilicities in aqueous solution then seem to represent the most attractive series for an initial investigation of the potential relationship between N_+ and *n*.

Ideally, second-order rate constants as a function of amine structure are required for a single substrate undergoing aminolysis *via* an S_N2 reaction at a saturated carbon atom in order to define a scale of *n* values for amine nucleophiles. Our search of the chemical literature has failed to locate any example of a single substrate for which a truly broad range of amine reactivities has been measured. Swain and Scott[2] defined *n* for only two amines (aniline and pyridine). Hall[5] evaluated literature data for the aminolysis of four epoxides and of chloroacetate ion and compiled *n* values for 38 primary, secondary and tertiary aliphatic amines and ammonia in aqueous solution. However, this list is not particularly comprehensive since it includes many *n*-alkylamines and *N*-methyl-*n*-alkylamines for which there is essentially no variation in *n* with the length of the alkyl chain. Hall's survey[5] did provide a list of eight aminolysis reactions, at both saturated and unsaturated carbon atoms, for which the *n* parameter appeared to be applicable, and this appears to be the most extensive application of the *n* parameter that is currently available for amine nucleophiles.

Subsequently, Koskikallio[6] defined *n* for 20 nitrogen nucleophiles (four aliphatic amines, two anilines, eleven nitrogen heteroaromatic species, ammonia, urea and acetamide) from their reactivities with methyl perchlorate in aqueous solution. This latter work also provided reactivities for these same nucleophiles and also several other anilines towards methyl perchlorate in methanolic solution. Pearson and coworkers[3] defined *n* for a large number of nucleophiles reacting with methyl iodide in methanol. This work included 14 amine nucleophiles of various structural types, but did not include a systematic variation by structure within any one class of amine nucleophiles. Gregory and Bruice[7] reported rate constants for the methylation of ten amines (including several α-effect amines) by methyl iodide in aqueous solution, Dixon and

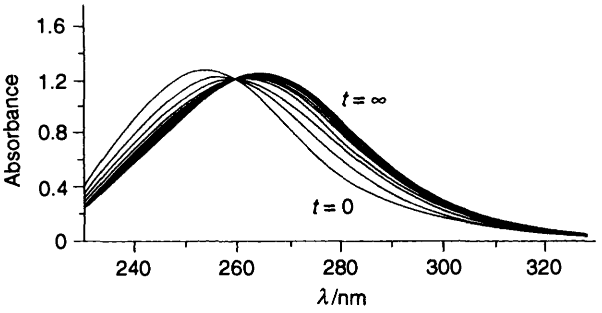


Fig. 1 Time-dependent spectra for the reaction of methyl 4-nitrobenzenesulfonate (0.1 mmol dm^{-3}) with morpholine buffer (193 mmol dm^{-3} morpholine + 96.5 mmol dm^{-3} HCl) in aqueous solution at pH 8.49 (at 25 °C). Successive spectral scans are at intervals of 60 s.

Bruice[8] reported kinetic data for the methylation of five amines by methyl toluene-*p*-sulfonate in aqueous solution and Knier and Jencks[9] have reported second-order rate constants for the reaction of 16 amines of various structural types with *N*-(methoxymethyl)-*N*,*N*-dimethylanilinium cations. This latter case represents a much more sterically hindered electrophilic carbon atom than in any of the other reactions cited above. Kinetic data for other S_N2 aminolysis reactions in aqueous solution are limited only to several amines in each case.

In the current work we have measured the second-order rate constants for the methylation of 91 amines (ammonia, 37 primary amines, 20 secondary amines, 29 tertiary amines and 4 α-effect amines) by methyl 4-nitrobenzenesulfonate (MNBS) in aqueous solution [eqn. (1)]. These data are analysed in terms of

$$O_2NC_6H_4SO_2OCH_3 + Nu \xrightarrow{k_{Nu}} O_2NC_6H_4SO_3^- + CH_3Nu^+ \quad (1)$$

amine basicity and steric effects in these amine nucleophiles. It is shown that careful selection of structural classes of amine is necessary for the confident assignment of accurate β_{nuc} parameters from Brønsted-type plots for S_N2 reactions. Although β_{nuc} is relatively invariant over various structural classifications for primary and secondary amines, this parameter does vary significantly with steric hindrance for tertiary amine nucleophiles. These data are then used to define the Swain–Scott *n* parameter for each of these 91 amines, and are also used to investigate fully the relationship between *n* and N_+ for this large group of neutral nitrogen nucleophiles by comparing the current rate data for an S_N2 reaction with the rate data in the accompanying paper[10] for nucleophilic addition to an sp^2-hybridized carbon atom in the 1-methyl-4-vinylpyridinium cation (MVP).

Results

The time-dependence of the electronic absorption spectrum of methyl 4-nitrobenzenesulfonate in an aqueous morpholine buffer solution is shown in Fig. 1. The absorption maximum at 254 nm in the spectrum of the ester is cleanly converted into a product spectrum having $\lambda_{max} = 265$ nm ($\log \varepsilon = 4.08$). This latter spectrum is consistent with that reported for the 4-nitrobenzenesulfonate anion.[11] Similar spectral observations were made for each amine investigated in the current study. The largest difference in the extinction coefficients of the reactant and product species occurs in the vicinity of 280 nm, and so the rates of all aminolysis reactions were monitored by following the time-dependence of the absorbance at this wavelength.

All reactions proved to be kinetically first order in sulfonate ester concentration for >4 reaction half-lives. Pseudo-first-order rate constants (k_{obs}) were measured for each amine at five amine concentrations covering a fivefold range of concentration. In all cases plots of k_{obs} *vs.* amine concentration ([Nu]) were linear [eqn. (2)] with a small ordinate intercept in the range (5–7) × 10^{-5} s^{-1}. This value is consistent with $k_{H_2O} = 6.25 \times 10^{-5}$ s^{-1} established[12] for the hydrolysis of MNBS in neutral aqueous solution at 25 °C. Second-order rate constants (k_{Nu}) for the aminolysis of MNBS by each amine were calculated from eqn. (2), and are listed in Table 1.

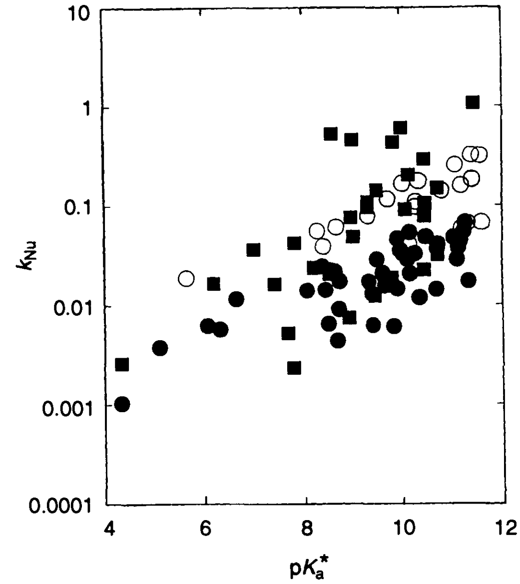


Fig. 2 Dependence of log k_{Nu} upon pK_a^* for all amines in the current study: ●, primary amines; ○, secondary amines; ■, tertiary amines

$$k_{obs} = k_{H_2O} + k_{Nu}[Nu] \quad (2)$$

A spectral change that is similar to that shown in Fig. 1 is also observed in basic aqueous solutions (pH = 12–13) of MNBS. Pseudo-first-order-rate constants for this reaction, measured at constant pH, are proportional to hydroxide ion concentration with a second-order rate constant of 6.8 × 10^{-3} dm^3 mol^{-1} s^{-1} for the base-catalysed hydrolysis of MNBS at 25 °C and ionic strength 0.1. Similar spectral changes are also observed in the presence of a variety of nucleophilic anions. Pseudo-first-order rate constants as a function of nucleophile concentration were linear functions of the concentration of the nucleophilic anion. Second-order rate constants for anionic nucleophiles are collected in Table 2.

Discussion

The dependence of k_{Nu} upon amine basicity [expressed as the statistically corrected acidity of the ammonium ion conjugate acids; $pK_a^* = pK_a + \log(p/q)$] is displayed in Fig. 2 for all amines investigated in the current work. This figure indicates that in general relative reactivities for a particular amine basicity lie in the order: tertiary > secondary > primary. There are exceptions to this general order, with some tertiary amines (especially those for which pronounced steric hindrance is expected at the nucleophilic nitrogen atom) being much less reactive than is consistent with this order.

In the accompanying paper,[10] we show that it is necessary to classify amines in terms of strictly defined structural classes in order to identify useful linear free energy relationships and β_{nuc} parameters for the nucleophilic attack of amines upon the 1-methyl-4-vinylpyridinium cation. It is clear from Fig. 2 that no single correlation equation is applicable to the data for the reactions of each of these major classes (*i.e.*, primary, secondary

Table 1 Second-order rate constants for the aminolysis of methyl 4-nitrobenzenesulfonate[a]

No.	Amine	Class[b]	pK_a^{*}[c]	k_{Nu}/dm^3 mol^{-1} s^{-1}	n[d]
1	NH_3		9.84	0.006 06	4.10 (4.23)[e] (4.16)[g]
2	CH_3NH_2	1A	11.27	0.067	5.21 (5.21)[e]
3	$CH_3(CH_2)_3NH_2$	1A	11.25	0.054 7	5.11 (5.04)[f] (5.13)[g]
4	$CH_3CH_2NH_2$	1A	11.18	0.043 3	5.01 (4.93)[e]
5	${}^{-}O_2C(CH_2)_3NH_2$	1A	11.04	0.047 8	5.05
7	${}^{-}O_2C(CH_2)_2NH_2$	1A	10.72	0.040 5	4.98
8	$HO(CH_2)_3NH_2$	1A	10.71	0.036 8	4.93
9	$H_2N(CH_2)_2NH_2$	1A	10.26	0.032 8[h]	4.88
10	$C_6H_5(CH_2)_2NH_2$	1A	10.48	0.048 5	5.06
11	$HO(CH_2)_2NH_2$	1A	10.12	0.028 7	4.82
12	$CH_3O(CH_2)_2NH_2$	1A	10.03	0.032 7	4.88
13	${}^{-}O_3S(CH_2)_2NH_2$	1A	9.49	0.028 8	4.82
14	$H_3{}^{+}N(CH_2)_3NH_2$	1A	9.66	0.015 7	4.54
15	$H_3{}^{+}N(CH_2)_2NH_2$	1A	8.06	0.010 4	4.35
16	$CF_3CH_2NH_2$	1A	6.32	0.005 78	4.08
17	Cyclohexylamine	1B	11.14	0.037 5	4.94
18	$(CH_3)_2CHNH_2$	1B	11.11	0.028 5	4.81 (4.68)[f]
19	$HOCH_2CH(CH_3)NH_2$	1B	9.91	0.014 6	4.51
20	$(HOCH_2)_2CHNH_2$	1B	9.38	0.013 0	4.45
21	$(CH_3)_3CNH_2$	1C	11.34	0.017 2	4.58 (4.15)[f]
22	$HOCH_2C(CH_3)_2NH_2$	1C	10.35	0.011 8	4.41
23	$(HOCH_2)_2C(CH_3)NH_2$	1C	9.41	0.006 29	4.12
24	$(HOCH_2)_3CNH_2$	1C	8.68	0.004 40	3.95
25	${}^{-}O_2CCH_2NH_2$	1D	10.16	0.053 8	5.11
26	$CH_2{=}CHCH_2NH_2$	1D	9.97	0.035 5	4.92 (4.92)[f]
27	$C_6H_5CH_2NH_2$	1D	9.91	0.046 5	5.04 (4.92)[f]
28	Gly–Gly	1D	8.73	0.017 4	4.59
29	$HC{\equiv}CHCH_2NH_2$	1D	8.63	0.021 7	4.69
30	$H_2NCOCH_2NH_2$	1D	8.55	0.022 3	4.72
31	Gly–Gly–Gly	1D	8.44	0.014 2	4.49
32	$N{\equiv}CCH_2NH_2$	1D	6.07	0.006 30	4.12
33	Alanine	1E	10.17	0.020 6	4.66
34	Serine	1E	9.63	0.019 9	4.65
35	Glutamine	1E	9.61	0.020 9	4.67
36	Asparagine	1E	9.32	0.017 2	4.58
37	Ala–Gly	1E	8.72	0.009 11	4.29
38	$H_2NCOCH(CH_3)NH_2$	1E	8.50	0.006 48	4.13
39	${}^{-}O_2CC(CH_3)_2NH_2$	1F	10.68	0.014 3	4.50
40	H_2NNH_2	1G	8.38	0.024 6[h]	4.75 (5.34)[f]
41	$HONH_2$	1G	6.65	0.011 6	4.40
42	CH_3ONH_2	1G	5.10	0.003 8	3.88
43	$H_2NCONHNH_2$	1G	4.34	0.001 04	3.28
45	$(CH_3)_2NH$		11.08	0.255	5.83 (5.63)[e]
46	$CH_3(CH_2)_3NHCH_3$	2A	11.20	0.158	5.60
47	$CH_3NH(CH_2)_3NHCH_3$	2A	10.80	0.140[h]	5.55
48	$CH_3NH(CH_2)_2NHCH_3$	2A	10.29	0.109[h]	5.43
49	$HO(CH_2)_2NHCH_3$	2A	10.28	0.096 7	5.38
50	$N{\equiv}C(CH_2)_2NHCH_3$	2A	8.40	0.038 8	4.96
52	$(CH_3)_2CHNHCH_3$	2B	11.20	0.058 6	5.15
53	${}^{-}O_2CCH_2NHCH_3$	2D	10.35	0.175	5.65
54	$C_6H_5CH_2NHCH_3$	2D	10.03	0.166	5.63
55	$N{\equiv}CCH_2NHCH_3$	2D	5.65	0.018 8	4.62
57	$(CH_3CH_2)_2NH$	2H	11.32	0.066 1	5.20 (4.75)[e]
58	$(CH_3CH_2CH_2)_2NH$	2H	11.30	0.066 5	5.21 (4.75)[f]
59	$HO(CH_2)_2NHCH_2CH_3$	2H	10.15	0.040	4.97
61	Pyrrolidine		11.57	0.313	5.92 (5.67)[f,g]
62	Piperidine	2J	11.42	0.180	5.67 (5.59)[e]
63	Perhydroazepine		11.41	0.182	5.67 (5.43)[f]
65	Piperazine	2J	9.72	0.116[h]	5.46 (5.59)[f]
66	Thiamorpholine	2J	9.30	0.078 7	5.28
67	Morpholine	2J	8.66	0.060 9	5.16 (5.29)[f] (5.13)[g]
68	4-Formylpiperidine	2J	8.27	0.055 6	5.12
73	$(CH_3)_3N$		9.85	0.434	6.07 (6.01)[e]
74	$CH_3CH_2N(CH_3)_2$	3A	10.16	0.202	5.72 (5.44)[e]
75	$(CH_3)_2N(CH_2)_3N(CH_3)_2$	3A	9.50	0.142[h]	5.56
76	$HO(CH_2)_2N(CH_3)_2$	3A	9.31	0.108	5.43 (5.20)[e]
77	$HO(CH_2)_3N(CH_3)_2$	3A	9.30	0.096 4	5.38
78	$(CH_3)_2N(CH_2)_2N(CH_3)_2$	3A	8.96	0.076	5.27
79	$(CH_3)_2{}^{+}NH(CH_2)_3N(CH_3)_2$	3A	7.81	0.042 1	4.99
80	$N{\equiv}CCH_2CH_2N(CH_3)_2$	3A	7.00	0.036 8	4.93
81	$(CH_3)_2{}^{+}NH(CH_2)_2N(CH_3)_2$	3A	6.20	0.016 6	4.56
82	$C_6H_{11}N(CH_3)_2$[i]	3B	10.72	0.149	5.58

(*contd.*)

Table 1 (*continued*)

83	$(CH_3)_2CHN(CH_3)_2$	3B	10.47	0.105	5.42 (4.85)[e]
84	$(CH_3CH_2)_2NCH_3$	3H	10.46	0.078 8	5.28 (4.80)[e]
85	$(HOCH_2CH_2)_2NCH_3$	3H	8.52	0.020 5	4.66
86	$(CH_3CH_2)_3N$	3I	10.72	0.031 9	4.87 (4.09)[e] (3.98)[g]
87	$HOCH_2CH_2N(CH_2CH_3)_2$	3I	9.80	0.018 7	4.62
88	$(HOCH_2CH_2)_2NCH_2CH_3$	3I	8.92	0.007 46	4.19
89	$(HOCH_2CH_2)_3N$	3I	7.78	0.002 36	3.66 (3.85)[e]
90	*N*-Methylpyrrolidine		10.46	0.290	5.89
91	*N*-Methylpiperidine	3J	10.08	0.091 2	5.35
92	*N*,*N*′-Dimethylpiperazine	3J	8.20	0.023 7[h]	4.73
93	*N*-Methylmorpholine	3J	7.41	0.016 3	4.56
94	*N*,*N*′-Dimethylpiperazinium cation	3J	4.34	0.002 62	3.71
95	*N*-Methyl 3-hydroxypiperidine		9.00	0.048 6	5.06
96	*N*-Ethylpiperidine	3L	10.45	0.022 5	4.70
97	*N*-(2-Hydroxyethyl)piperidine	3L	9.45	0.012 3	4.43
98	*N*-Ethylmorpholine	3L	7.67	0.005 22	4.03
99	Quinuclidine	3M	11.45	1.06	6.48
100	3-Hydroxyquinuclidine	3M	10.02	0.607	6.23
101	3-Chloroquinuclidine	3M	9.03	0.458	6.10

[a] In aqueous solution at 25 °C, ionic strength 0.1 mol dm^{-3}. [b] Amine numbers and classes correspond to those in the accompanying work.[10] [c] $pK_a^* = pK_a + \log(p/q)$ where p is the number of equivalent protons in the ammonium ion conjugate acid, and q is the number of equivalent basic sites in the amine; pK_a values are from ref. 13. [d] Calculated from eqn. (4). [e] n defined for this amine by Hall[5] from aminolysis reactions of epoxides in aqueous solution. [f] n defined for this amine by Hall[5] from aminolysis reactions of 2,4-dinitrochlorobenzene in ethanol solution, but referenced to reactions in water. [g] n defined for this amine by Koskikallio[6] from aminolysis of methyl perchlorate in water. [h] Statistically corrected for two equivalent nucleophilic sites; n for this amine is also based upon this statistically corrected value. [i] *N*,*N*-Dimethylcyclohexylamine.

Table 2 Second-order rate constants for the reaction of anionic nucleophiles and simple amines with methyl 4-nitrobenzenesulfonate[a] and with methyl iodide[b]

	$k_{Nu}/dm^3\ mol^{-1}\ s^{-1}$		
Nucleophile	$CH_3OSO_2C_6H_4NO_2$	CH_3I	n[c]
Thiosulfate	7.0×10^{-2}	2.84×10^{-2}	6.35
Cyanide	1.8×10^{-2}	5.76×10^{-4}	5.13
Hydroxide	6.9×10^{-3}	6.36×10^{-5}	4.23
Iodide	3.9×10^{-3}	4.71×10^{-4}	4.93
Thiocyanate	3.0×10^{-3}	3.58×10^{-4}	4.80
Azide	2.3×10^{-3}		3.92
Bromide	5.8×10^{-4}	4.16×10^{-5}	4.02
Ammonia	6.1×10^{-3}	9.5×10^{-5}	4.23
Methylamine	6.7×10^{-2}	2.2×10^{-3}	5.21
Dimethylamine	0.255	9.2×10^{-3}	5.63
Trimethylamine	0.434	2.4×10^{-2}	6.01
Water[d]	1.1×10^{-6}	1.3×10^{-9}	0

[a] In aqueous solution at 25 °C, ionic strength 0.1 mol dm^{-3}; data from the current study. [b] From ref. 18 for anionic nucleophiles at 25 °C; by interpolation at 25 °C using the Arrhenius parameters reported[17] for amines with methyl iodide. [c] From ref. 19 for anionic nucleophiles and from ref. 5 for amines. [d] Second-order rate constants calculated from $k_{H_2O}/55.5$ using the pseudo-first-order rate constants reported by Robertson.[12]

and tertiary) of amines with MNBS, and we have therefore adopted the same structure-based subclassifications of primary and secondary amines that we defined in the accompanying work. We have also adopted an analogous set of classifications for tertiary amines which were not considered in detail previously, since nucleophilic attack is not the rate-determining step in the addition of these species to the 1-methyl-4-vinylpyridinium cation. Within these structural classes, clean linear relationships are discernible in Figs. 3–5, with β_{nuc} values as listed in Table 3.

Primary Amines.—The influence of substitution upon the α-carbon atom of primary amines is demonstrated in Fig. 3 for the three series 1A, 1B and 1C. Within these three series of amines, increasing substitution at the α-carbon atom leads to a progressive decrease in reactivity at constant pK_a^*. Interpolation in the Brønsted correlations of Table 3 indicates that $k_{Nu,10}$ (which is the second-order rate constant for an amine nucleophile of $pK_a^* = 10.0$) is in the ratio 1 : 0.53 : 0.28 for 1A, 1B and 1C, respectively. For these three series of amines β_{nuc} appears to be identical within experimental error.

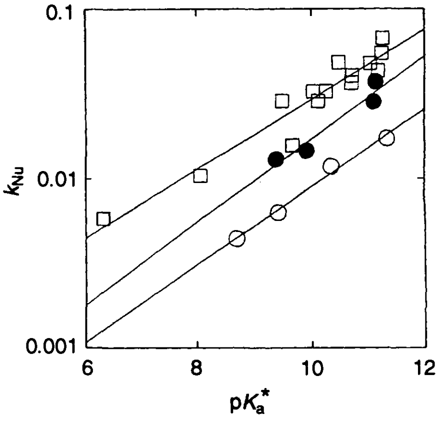


Fig. 3 Brønsted-type plots for the reactions of primary amines with methyl 4-nitrobenzenesulfonate: □, class 1A amines; ●, class 1B amines; ○, class 1C amines

For the addition of amines to the 1-methyl-4-vinylpyridinium cation (MVP) we have shown[10] that there is a significant difference in reactivity between amines having an sp^2- or sp-hybridized β-carbon atom and those having an sp^3-hybridized β-carbon atom. The former class (*e.g.*, 1D) had $k_{Nu,10}$ 1.9 times greater for attack on MVP than did class 1A amines. A similar distinction between amines of classes 1A and 1D for nucleophilic attack on MNBS does not appear to be supported by the Brønsted correlations in Table 3, since both β_{nuc} and log k_o are identical to within experimental error for these two classes of amine, although the interpolated $k_{Nu,10}$ is 30% larger for 1D than for 1A. The statistical parameters for the combination of 1A + 1D primary amines (Table 3) are also poorer than for these two classes of amine considered

Table 3 Parameters for Brønsted-type correlations for aminolysis of methyl 4-nitrobenzenesulfonate

Amine type	Class	β_{nuc}	$\log k_o$	r	n	$k_{Nu,10}$[a]	$k^{rel}_{Nu,10}$
$XCH_2CH_2NH_2$	1A	0.21 (±0.02)	−3.59 (±0.09)	0.959	14	0.032	(1)
$(XCH_2)_2CHNH_2$	1B	0.24 (±0.04)	−4.21 (±0.07)	0.967	4	0.017	0.53
$(XCH_2)_3CNH_2$	1C	0.23 (±0.02)	−4.34 (±0.04)	0.994	4	0.0091	0.28
$(sp^2/sp)C{-}CH_2NH_2$	1D	0.22 (±0.02)	−3.60 (±0.09)	0.965	8	0.041	1.3
	1A + 1D	0.19 (±0.02)	−3.4 (±0.1)	0.939	22		
$(sp^2)C{-}CH(CH_2X)NH_2$	1E	0.32 (±0.06)	−4.86 (±0.09)	0.927	6	0.024	0.74
	1B + 1E	0.23 (±0.04)	−4.06 (±0.09)	0.916	10		
$(sp^2)C{-}C(CH_2X)_2NH_2$	1F				1	0.009[b]	0.27
α-Effect amines	1G	0.32 (±0.06)	−4.2 (±0.2)	0.963	4	0.098	3.1
$XCH_2CH_2NHCH_3$	2A	0.22 (±0.01)	−3.28 (±0.03)	0.995	5	0.083	2.6
$(XCH_2)_2CHNHCH_3$	2B				1	0.032[c]	1.0
$(sp^2/sp)C{-}CH_2NHCH_3$	2D	0.21 (±0.01)	−2.91 (±0.03)	0.999	3	0.154	4.8
$(XCH_2CH_2)_2NH$	2H	0.19 (±0.01)	−3.32 (±0.01)	0.999	3	0.038	1.2
$X(CH_2CH_2)_2NH$	2J	0.17 (±0.02)	−2.65 (±0.05)	0.979	5	0.112	3.5
$XCH_2CH_2N(CH_3)_2$	3A	0.25 (±0.02)	−3.31 (±0.07)	0.983	8	0.154	4.8
$(XCH_2)_2CHN(CH_3)_2$	3B				2	0.080[d]	2.5
$(XCH_2CH_2)_2NCH_3$	3H	(0.30)	(−4.24)		2	0.058	1.8
$(XCH_2CH_2)_3N$	3I	0.39 (±0.03)	−5.64 (±0.07)	0.993	4	0.018	0.56
$X(CH_2CH_2)_2NCH_3$	3J	0.27 (±0.01)	−3.75 (±0.05)	0.998	4	0.089	2.8
$X(CH_2CH_2)_2NCH_2CH_2X$	3L	0.23 (±0.01)	−4.02 (±0.03)	0.998	3	0.019	0.59
3-X-Quinuclidines	3M	0.15 (±0.01)	−1.72 (±0.02)	0.996	3	0.60	19

[a] From the Brønsted-type plot at $pK_a^* = 10.0$; units: $dm^3\ mol^{-1}\ s^{-1}$. [b] Calculated from k_{Nu} for amine No. 39 in Table 3, by assuming $\beta_{nuc} = 0.32$ as for class 1E amines. [c] Calculated from k_{Nu} for amine No. 52 in Table 3, by assuming $\beta_{nuc} = 0.22$ as for class 2A amines. [d] Calculated from k_{Nu} for amine No. 83 in Table 3, by assuming $\beta_{nuc} = 0.25$ as for class 3A amines.

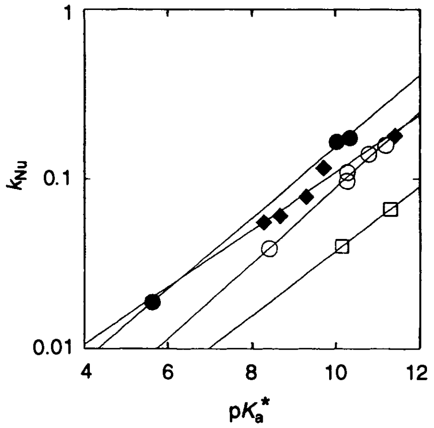


Fig. 4 Brønsted-type plots for the reactions of secondary amines with methyl 4-nitrobenzenesulfonate: ○, class 2A amines; ●, class 2D amines; □, class 2H amines; ◆, class 2J amines

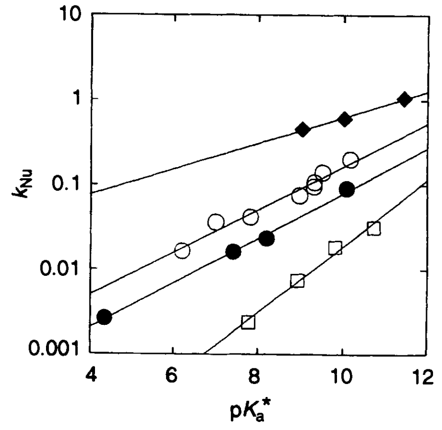


Fig. 5 Brønsted-type plots for the reactions of tertiary amines with methyl 4-nitrobenzenesulfonate: ○, class 3A amines; □, class 3I amines; ●, class 3J amines; ◆, class 3M amines

individually. Similar observations are found for amines of classes 1B and 1E. The data for the only class 1F amine is also consistent with the data for class 1C amines. The evidence for a special β-effect for amines having an sp^2- or sp-hybridized β-carbon atom is thus weak for primary amines. However, an enhanced reactivity for class 2D *N*-methyl secondary amines relative to class 2A *N*-methyl secondary amines is clearly established by the correlations in Table 3.

α-Effect amines are 3.1 times more reactive than class 1A amines for reactions with MNBS. However, as expected,[7,8] this enhanced reactivity for α-effect amines with the saturated carbon electrophile in MNBS is considerably smaller than the 12-fold rate enhancement observed[10] for these α-effect amines in reactions with the sp^2-electrophilic carbon centre in the 1-methyl-4-vinylpyridinium cation.

Secondary Amines.—Structural variations within secondary amines are of two types. Classes 2A and 2D demonstrate the effect of keeping one *N*-alkyl substituent constant (*N*-methyl in these two cases) and changing the structure of the other *N*-alkyl substituent, whereas classes 2H and 2J demonstrate the effect of simultaneous structural variation of both substituents on nitrogen. As noted above, the distinction between amines of classes 2A and 2D appears to be retained (Fig. 4 and Table 3) despite the merging of the data for 1A and 1D primary amines that is discussed above for reactions with MNBS.

The six-membered ring endocyclic secondary amines (class 2J) are three times more reactive than the corresponding *N*,*N*-dialkyl amines (class 2H), and also slightly more reactive than *N*-methyl-*N*-alkylamines (class 2A) (Fig. 4 and Table 3). Variation of reactivity with ring-size for endocyclic secondary amines may be summarized by: pyrrolidine > piperidine ≈ perhydroazepine > *N*,*N*-diethylamine = *N*,*N*-dipropylamine, with a fivefold variation in reactivity in this series.

Tertiary Amines.—*N*,*N*-Dimethylalkylamines (class 3A) are 4.8 times more reactive than primary alkylamines (class 1A) and 1.8 times more reactive than secondary *N*-methylalkylamines (class 2A). The relative reactivities at $pK_a^* = 10$ decrease in the order *N*,*N*-dimethylalkylamines (class 3A) > *N*,*N*-dialkylmethylamines (class 3H) > *N*,*N*,*N*-trialkylamines (class 3I)

Table 4 Correlation of second-order rate constants for S_N2 reactions in aqueous solution with data for the aminolysis of methyl 4-nitrobenzenesulfonate (MNBS)

$$\log k_{Nu}(RX) = (\text{slope}) \log k_{Nu}(MNBS) + \log k_o$$

RX	Slope	$\log k_o$	r	n	Amines[a]
$^-O_2CCH_2Cl$[b]	1.17 (±0.21)	−2.83 (±0.31)	0.914	8	1, 2, 4, 45, 57, 58, 73, 86
Propylene oxide[c]	1.02 (±0.13)	−2.22 (±0.23)	0.912	13	1, 2, 3, 4, 21, 45, 57, 73, 74, 76, 83, 84, 86
$3\text{-}NO_2C_6H_4\overset{+}{N}(CH_3)_2CH_2OCH_3$[d]	0.61 (±0.07)	−2.05 (±0.15)	0.964	8	3, 12, 41, 42, 45, 67, 99, 102
Ethylene oxide[e]	0.90 (±0.07)	−1.73 (±0.12)	0.976	10	4, 9, 15, 25, 28, 40, 43, 57, 62, 86
CH_3I[f]	1.21 (±0.06)	−0.99 (±0.12)	0.990	11	1, 2, 16, 25, 40, 41, 42, 45, 62, 67, 73
$CH_3OSO_2C_6H_4(4\text{-}CH_3)$[g]	1.04 (±0.23)	−0.57 (±0.21)	0.933	5	16, 25, 28, 40, 42
CH_3OClO_3[h]	0.72 (±0.15)	−0.61 (±0.19)	0.936	5	1, 3, 61, 67, 86
$CH_3OSO_2C_6H_4(4\text{-}NO_2)$[i]	1.0	0.0		92	

[a] Identified by numbers from Table 1. [b] Data (at 25 °C) from ref. 14. [c] Data (at 20 °C) from ref. 15 as quoted by Hall.[5] Ref. 15 also contains less extensive data sets for the aminolysis of glycidol, epichlorohydrin and ethylene oxide. [d] Data (at 25 °C) from ref. 9. [e] Data (at 25 °C) from ref. 16. [f] Data (at 30 °C) from ref. 7 for all amines except ammonia, dimethylamine and trimethylamine which are from ref. 17. [g] Data (at 30 °C) from ref. 8. [h] Data (at 0 °C) from ref. 6. [i] Current study.

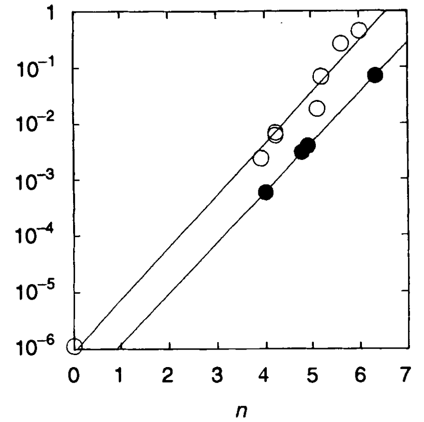


Fig. 6 Swain–Scott plots for the reactions of light-atom nucleophiles [○, eqn. (4)] and heavy-atom nucleophiles [●, eqn. (5)] with methyl 4-nitrobenzenesulfonate (data from Table 2)

(8.6:3.2:1 for alkyl > methyl). The 3-substituted quinuclidines (class 3M) represent by far the most reactive class of amines in the current study. The quinuclidines are 34 times more reactive than trialkylamines (class 3I) and seven times more reactive than *N*-methyl six-membered endocyclic tertiary amines (class 3J). *N*-Alkyl six-membered endocyclic tertiary amines (class 3L, alkyl > methyl) are 4.7 times less reactive than the corresponding *N*-methyl series (class 3J).

The comparison of the various classes of tertiary amines in Table 3 reveals a tendency for β_{nuc} to increase with decreasing reactivity. Thus $k_{Nu,10}$ varies in the order, 3M > 3A > 3J > 3H > 3I while β_{nuc} varies in the opposite direction from 0.15 to 0.39. Since the variation in reactivity appears to be mainly a steric effect at the nucleophilic centre, this order implies that β_{nuc} increases with increasing steric hindrance in the nucleophile. The class 3L amines appear to represent an exception to this generalization; there is no obvious structural reason for this exception.

Comparison with Other S_N2 *Reactions in Aqueous Solution.*— There have been relatively few previous reports of rate data for extended series of amine nucleophiles in S_N2 reactions in aqueous solution. Table 4 summarizes the correlation equations between literature data for such reactions and our current data for the aminolysis of MNBS. In general, reasonable linear relationships are apparent for a variety of leaving groups (*N*,*N*-dimethyl-3-nitroaniline, iodide ion, perchlorate ion, chloride ion and alkoxide ions in the ring-opening of epoxides). Several of the statistically poor correlations arise from the inclusion of triethylamine which often shows the largest deviation from the correlation based upon other amines. This is presumably a steric phenomenon, since triethylamine is usually the most hindered amine in these series of aminolysis reactions.

The slopes of the correlations in Table 4 vary in the range 0.6–1.2; such variable slopes must ultimately be interpreted in terms of variations in the detailed transition-state structures in these S_N2 reactions. There is no systematic relationship between slope and reactivity for the reactions listed in Table 4. Of course, in view of the variety of types of electrophilic carbon centre and leaving groups involved, it would have been truly remarkable if any such systematic relationship were to be found. The substrates included in Table 4 cover over a 1000-fold range in reactivity; methyl perchlorate is the only species that is more reactive (after correction for temperature) than methyl 4-nitrobenzenesulfonate of the current study.

The smallest slope of 0.61 for the *N*-methoxymethyl-*N*,*N*-dimethyl-3-nitroanilinium cation (**1**) is associated with a carbocation-like transition state for substitution at the methylene carbon of this substrate.[9] The correlation of the data for the aminolysis of this anilinium cation with the data for the aminolysis of MNBS is remarkable in view of the significant differences in steric, electronic and solvation factors which influence the transition-state structures in these two reactions. Such a correlation for a diverse (although numerically small) group of amines [two primary amines (propylamine and 2-methoxyethylamine), two secondary amines (dimethylamine and morpholine), two tertiary amines (quinuclidine and 1,4-diazabicyclooctane), hydroxylamine and methoxylamine] reinforces the premise of the current study that systematic structural effects upon amine nucleophilicities towards sp^3-hybridized carbon should ultimately be deducible. We note, however, that anionic nucleophiles (I^-, Br^-, N_3^-, HO^-, ^-CN) deviate dramatically from the amine correlation, presumably because of important electrostatic interactions between these anions and **1**.

$$3\text{-}NO_2C_6H_4N^+(CH_3)_2CH_2OCH_3$$

1

Data for the dependence of log k_{Nu} upon Swain–Scott nucleophilicity parameters (n) are collected in Table 2 for both amine and anionic nucleophiles in S_N2 reactions with both methyl 4-nitrobenzenesulfonate and methyl iodide.[17,18] We have used Koskikallio's n values[19] for anionic nucleophiles and Hall's n values[5] for amine nucleophiles. Both of these data sets of nucleophilicities are ultimately based on the original definition of n by Swain and Scott[2] in terms of the reactivity of methyl bromide towards these nucleophiles. For reactions with methyl iodide, both amine and anionic nucleophiles can be accommodated by a single correlation [eqn. (3)]. The slope

$$\log k_{\mathrm{Nu}}(\mathrm{MeI}) = 1.19\,(\pm 0.03)\,n - 9.1\,(\pm 0.2) \qquad (r = 0.996; n = 13) \quad (3)$$

(s = 1.19) for this correlation is similar to that deduced for reactions of methyl iodide by other workers for more limited sets of nucleophiles.[20–22]

For the reactions of methyl 4-nitrobenzenesulfonate, however, two distinct correlations with n are apparent (Fig. 6). The reactions of amine nucleophiles, water, hydroxide ion and azide ion are described by eqn. (4) (cyanide ion appears to be slightly less reactive than predicted by the data for the other light-atom nucleophiles), while the iodide, bromide, thiocyanate and thiosulfate ions require eqn. (5). This latter group of heavy-atom (I, Br and S) anionic nucleophiles are five times less reactive towards methyl 4-nitrobenzenesulfonate than are the light-atom (O, N and C) nucleophiles. Since each of these reactions involves nucleophilic attack upon an electrically neutral monosubstituted methane derivative, these data clearly indicate the importance of the leaving group in determining relative nucleophilicities towards an electrophilic carbon atom. Koskikallio made a similar observation[19] for the reactivities of anionic nucleophiles towards methyl perchlorate in aqueous solution; water, acetate, hydrogenphosphate, azide, hydroxide, cyanide and thiosulfate anions being described by a single correlation with s = 0.83 while chloride, bromide, thiocyanate and iodide anions were of somewhat lower reactivity (fourfold on average) with s = 1.06. Koskikallio referred to these two groups as basic and non-basic nucleophiles, respectively. In fact the data point for thiosulfate lies exactly at the intersection of these two correlations for methyl perchlorate, and so the alternative classification of thiosulfate with the latter 'non-basic' group leads to the same light-atom and heavy-atom nucleophile sets which we describe above for the reactions of methyl 4-nitrobenzenesulfonate.

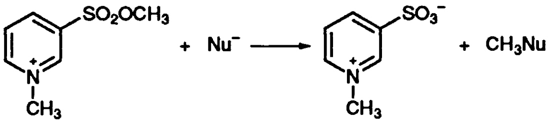
For light-atom nucleophiles:

$$\log k_{\mathrm{Nu}}(\mathrm{MNBS}) = 0.92\,(\pm 0.05)\,n - 6.06\,(\pm 0.23) \qquad (r = 0.992; n = 8) \quad (4)$$

For heavy-atom nucleophiles:

$$\log k_{\mathrm{Nu}}(\mathrm{MNBS}) = 0.89\,(\pm 0.01)\,n - 6.83\,(\pm 0.01) \qquad (r = 0.999; n = 4) \quad (5)$$

Ash and co-workers[23] have reported rate data for the methylation of many anionic nucleophiles with the 1-methyl-3-methoxysulfonylpyridinium cation (**2**). This cation ($k_{\mathrm{H_2O}}$ = 8.18×10^{-4} s^{-1} at 25 °C) is 13 times more reactive towards water than is MNBS ($k_{\mathrm{H_2O}} = 6.25 \times 10^{-5}$ s^{-1}).[12] Although these workers did not analyse their data in this way, it is clear that light-atom nucleophiles (H_2O, NO_3^-, F^-, SO_4^{2-}, $CH_3CO_2^-$, HCO_3^-, N_3^-) and heavy-atom nucleophiles (Cl^-, Br^-, ^-SCN, I^-, $S_2O_3^{2-}$) do fit different correlation lines. It should be noted for **2** that the data point for hydroxide ion appears to be approximately ten times too large relative to the data for other light-atom nucleophiles, and that the data point for $S_2O_3^{2-}$, as also mentioned above for reactions of methyl perchlorate, appears to be common to both correlation lines. Similar differentiation of light- and heavy-atom nucleophiles is found in the rate data for the attack of nucleophilic anions upon methyl benzenesulfonate[24] and methyl nitrate.[25]



2

(6)

The difference in reactivities between light- and heavy-atom nucleophiles is most likely a polarizability phenomenon. Edwards[26,27] recognized that polarizability was an important component of nucleophilicity and developed a quantitative description of this phenomenon. The requirement for different classes of nucleophile towards methyl 4-nitrobenzenesulfonate but not for reactions with methyl iodide [Fig. 6 and eqns. (3)–(5)] is consistent with Pearson and Songstad's expectation[28] of a 'symbiotic effect' between attacking nucleophiles and the leaving group in S_N2 reactions. In terms of their classification of hard and soft bases, the prediction is that higher rates will be found when the nucleophile and nucleofuge are either both hard or both soft. Thus the reactions of hard-base nucleophiles (H_2O, HO^-, amines) with a substrate having a hard sulfonate anion nucleofuge are expected to be faster than for soft-base nucleophiles (I^-, ^-SCN, $S_2O_3^{2-}$, Br^-) reacting with this same species. It is interesting that azide ion, which is classified as a borderline hard/soft base, and cyanide ion which is classified as a soft base, seem to belong to the general class of hard base nucleophiles in reactions with MNBS. For this reason, we prefer our own description of these data that was introduced above in terms of light and heavy nucleophilic atoms. The definition of n in terms of the reactivity of methyl bromide, which has a soft base nucleofuge, makes no allowance for this distinction between classes of nucleophile and consequently such distinctions will not appear for other soft-base nucleofuges (*e.g.*, iodide ion). Note however, that the distinction between nucleophile classes does appear with other hard-base leaving groups such as perchlorate ion and nitrate ion and also other sulfonate anions (see above). As a caveat to these nucleophile classifications, it should be noted that no clear-cut difference between light- and heavy-atom nucleophiles is apparent in the nucleophilic substitution reactions of several 4-nitrobenzyl sulfonates[29] or of 1-(4-nitrophenyl)-2-propyl toluene-*p*-sulfonate,[30] although in each of these cases several nucleophiles (azide, cyanide and even hydroxide occasionally) do show dramatic deviations from Swain–Scott correlations for other nucleophiles.

The slopes of the correlations in eqns. (4) and (5) are similar to s = 0.86 (at 25 °C)[31] reported for methyl methanesulfonate and also for s for a variety of other methyl alkanesulfonates,[32] and establish that nucleophilic attacks upon the methyl esters of sulfonic acids are, in general, less sensitive to nucleophilicity than are the corresponding reactions of methyl bromide (s = 1.0 by definition) and methyl iodide [s = 1.19 in eqn. (3) above]. A similar observation has been made for the reactions of 1-(4-nitrophenyl)-2-propyl toluene-*p*-sulfonate, bromide and iodide.[30]

Comparison of Nucleophilicities towards sp^2- *and* sp^3-*Hybridized Carbon*.—The rate constants for the addition of amines to the 1-methyl-4-vinylpyridinium cation (MVP) in the accompanying study[10] and for the aminolysis of methyl 4-nitrobenzenesulfonate in this work represent the most comprehensive comparison that has been attempted to date of nucleophilic attack upon sp^2- and sp^3-hybridized carbon atoms. The relationship between all second-order rate constants that we have measured for these two reactions is indicated in Fig. 7. Only data for primary and secondary amines are considered in this comparison, since we have shown that nucleophilic attack is not the rate-determining step for the addition of tertiary amines to MVP. Least-squares fitting of the data in Fig. 7 for all 58 primary

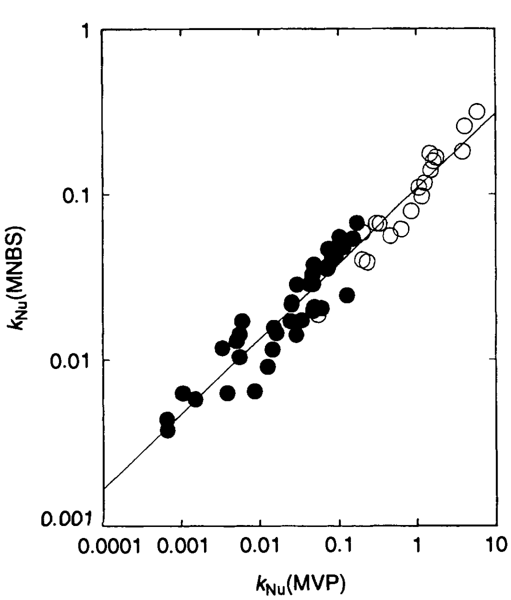


Fig. 7 Correlation of log k_{Nu} (MNBS) for the aminolysis of methyl 4-nitrobenzenesulfonate with log k_{Nu} (MVP) for amine addition to the 1-methyl-4-vinylpyridinium cation:[10] ●, primary amines; ○, secondary amines. The correlation line corresponds to eqn. (7).

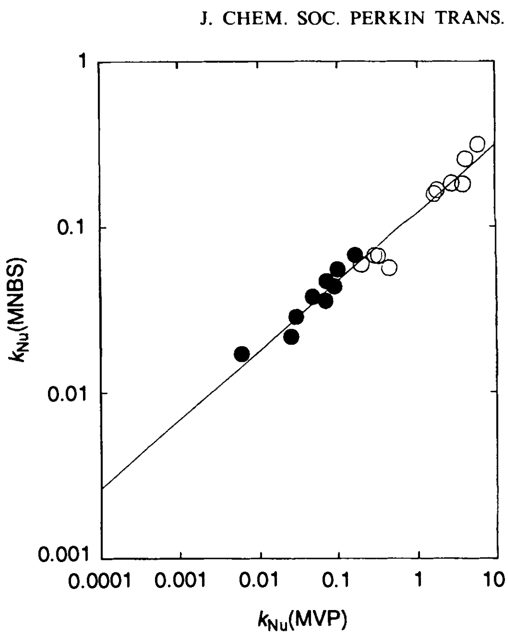


Fig. 8 Correlation of log k_{Nu} (MNBS) for the aminolysis of methyl 4-nitrobenzenesulfonate with log k_{Nu} (MVP) for amine addition to the 1-methyl-4-vinylpyridinium cation[10] for hydrocarbon amines only (see the text): ●, primary amines; ○, secondary amines. The correlation line corresponds to eqn. (8).

and secondary amines gives the correlation eqn. (7). The slope of

$$\log k_{Nu}\,(\text{MNBS}) = 0.44\,(\pm 0.02) \log k_{Nu}\,(\text{MVP}) - 0.96\,(\pm 0.12) \quad (r = 0.954;\, n = 58) \qquad (7)$$

the linear correlation in eqn. (7) is a reflection of the fact that β_{nuc} values for amine attack on the 1-methyl-4-vinylpyridinium cation[10] are, in general, approximately twice as large as β_{nuc} for aminolysis of methyl 4-nitrobenzenesulfonate (Table 3).

Careful inspection of Fig. 7 indicates that the 20 amines, both primary and secondary, that contain only alkyl substituents unsubstituted by electronegative atoms may lie on a slightly different correlation line [Fig. 8 and eqn. (8)] than do the 38 primary and secondary amines which contain one or more electronegative atoms [eqn. (9)]. Analysis of the data for the heteroatom amines using a subset which includes only 23 neutral amine species gives eqn. (10).

For hydrocarbon amines:

$$\log k_{Nu}\,(\text{MNBS}) = 0.41\,(\pm 0.01) \log k_{Nu}\,(\text{MVP}) - 0.91\,(\pm 0.06) \quad (r = 0.991;\, n = 20) \qquad (8)$$

For heteroatom amines:

$$\log k_{Nu}\,(\text{MNBS}) = 0.43\,(\pm 0.02) \log k_{Nu}\,(\text{MVP}) - 1.02\,(\pm 0.11) \quad (r = 0.944;\, n = 38) \qquad (9)$$

For neutral heteroatom amines:

$$\log k_{Nu}\,(\text{MNBS}) = 0.42\,(\pm 0.02) \log k_{Nu}\,(\text{MVP}) - 1.04\,(\pm 0.11) \quad (r = 0.962;\, n = 23) \qquad (10)$$

The differences in the slope and intercept parameters of eqns. (8), (9) and (10) are probably not statistically significant, however, the quite different correlation coefficients for these groups of amines indicate a much greater scatter in the data for the heteroatom amines than for hydrocarbon-derived amines. This scatter is presumably a reflection of the greater structural variation present in the heteroatom amine class which includes anionic and cationic amines in addition to the neutral species. Despite the scatter for heteroatom amines, there is only one heteroatom amine ($CH_3NHCH_2CO_2^-$) which falls above the correlation line for the hydrocarbon amines. We also note that ammonia falls among the data for the hydrocarbon amines while the data point for the hydroxide ion nucleophile lies on the correlation line for the heteroatom amines [eqn. (9)].

We have also considered correlations of amine nucleophilicities towards MNBS and MVP for primary and secondary amines independently of one another. The 37 primary amines generate the correlation eqn. (11), whereas the 21 secondary amines produce eqn. (12). Although each of these correlations

For primary amines:

$$\log k_{Nu}\,(\text{MNBS}) = 0.44\,(\pm 0.03) \log k_{Nu}\,(\text{MVP}) - 0.95\,(\pm 0.12) \quad (r = 0.900) \qquad (11)$$

For secondary amines:

$$\log k_{Nu}\,(\text{MNBS}) = 0.57\,(\pm 0.03) \log k_{Nu}\,(\text{MVP}) - 0.98\,(\pm 0.08) \quad (r = 0.968) \qquad (12)$$

are statistically inferior to those for all amines in eqns. (8)–(10), there does appear to be an indication that the slope of the correlation eqn. (12) for secondary amines (0.57 ± 0.03) is somewhat larger than that for primary amines in eqn. (11) (0.44 ± 0.03). In considering whether these correlations indicate significant differences for primary and secondary amines it must be noted that there is little overlap in Fig. 7 between the data for primary and secondary amines. In general, secondary amines are more reactive towards both MNBS and MVP than are primary amines. Furthermore, the total ranges in reactivities that are observed for secondary amines towards MNBS (eightfold) and MVP (thirtyfold) are much smaller than for primary amines reacting with each of these two substrates (fifteenfold for MNBS and 260-fold for MVP). Thus any difference in the reactivities of hydrocarbon and heteroatom secondary amines as indicated above can be expected artificially to increase the slope of such correlations which include both hydrocarbon and heteroatom secondary amines.

We have shown that nucleophilic attack upon MVP correlates with Ritchie's N_+ parameter, while nucleophilic attack upon MNBS correlates with the Swain–Scott n parameter. The current data for primary, secondary and tertiary amines reacting with MNBS and for the reactions of primary and secondary amines with MVP in the accompanying work[10] represent reactions with the absolute minimum of steric hindrance at the electrophilic centre. We suggest that these data should be used as the basis for comprehensive scales of n and N_+ for amines in aqueous solution. To this end, we tabulated[10] a new set of N_+ parameters for primary and secondary amines based upon eqn. (13). We can now also use eqn. (4) deduced

$$N_+ = \log k_{\mathrm{Nu}}(\mathrm{MVP}) + 7.34 \qquad (13)$$

above to evaluate n for all amines in the current study; this new set of n parameters for amines is included in Table 1. The Brønsted correlations presented for the various amine classes reacting with MNBS (Table 3) and MVP[10] should also allow the estimation of k_{Nu} for other structurally related amines, and consequently of appropriate n and N_+ parameters for such species.

For most amines there is a close correspondence (see Table 1) between n defined in the current work and n defined by Hall[5] for 19 amines reacting with epoxides in aqueous solution. Hall also used the reaction of amines with 2,4-dinitrochlorobenzene in ethanol as a secondary source of n parameters for a further 20 amines. Despite the fact that this latter reaction is at an sp^2-carbon and in a non-aqueous solvent, in most cases there is also reasonable agreement between n defined in this way and n defined in the current study (Table 1). Four of the n parameters for amines that Koskikallio defined[6] for the aqueous aminolysis of methyl perchlorate are also similar to those of the current study. The major exception is n for triethylamine which we find to be considerably larger than previously reported. Pearson and coworkers[3] defined n for eight aliphatic amines from their reactions with methyl iodide in methanol. For these eight amines, the current n values in water are all smaller than n in methanol [by 1.3–2.2 units; *e.g.*, piperidine, $n(\mathrm{CH_3OH}) = 7.30$, $n(\mathrm{H_2O}) = 5.67$; triethylamine, $n(\mathrm{CH_3OH}) = 6.66$, $n(\mathrm{H_2O}) = 4.87$; hydroxylamine, $n(\mathrm{CH_3OH}) = 6.60$, $n(\mathrm{H_2O}) = 4.40$; ammonia, $n(\mathrm{CH_3OH}) = 5.50$, $n(\mathrm{H_2O}) = 4.10$].

Correlation equations such as eqns. (7)–(12) then indicate that, at least for amine nucleophiles, there is a reasonably close relationship between the n and N_+ parameters. However, the existence of subclasses such as the hydrocarbon and heteroatom amines proposed above, and the general scatter within the latter group of amines in particular, suggest that a single all-purpose parameter that will always accurately measure amine nucleophilicity may continue to be elusive. Nevertheless, an algebraic relationship between n and N_+ may be evaluated by substitution of eqns. (4) and (13) into eqn. (7). This leads to the relationship of eqn. (14), which might be further refined for more

$$N_+ = 2.1n - 4.3 \qquad (14)$$

limited groups of amines such as the hydrocarbon amines and heteroatom amines identified above by substitution into one of eqns. (8)–(12) instead of into eqn. (7).

Eqn. (14) may have some predictive usefulness to estimate N_+ parameters for tertiary amines which do not react with the 1-methyl-4-vinylpyridinium cation by rate-determining nucleophilic attack;[10] *e.g.*, $N_+ = 8.4$ for trimethylamine; $N_+ = 9.3$ for quinuclidine. However, note that eqn. (14) is not applicable to anionic nucleophiles; for instance, it is well established that in aqueous solution N_+ lies in the order,[33] sulfite (7.9) > azide (7.6) > hydroxide (4.75) > cyanide (3.67), whereas n for these four nucleophiles follows the order,[19] sulfite (5.67) > cyanide (5.13) > hydroxide (4.23) > azide (3.92).

To the best of our knowledge, the linear dependence between n and N_+ in eqn. (14) is the first quantitative expression of the interrelationship of these two nucleophilicity parameters. However, the fact that such a relationship exists is inherent in some correlations which have been presented in the literature. As we noted above, Hall[5] successfully correlated the rates of aminolysis of 1-chloro-2,4-dinitrobenzene in ethanol with n defined for aqueous solution. He also further extended this study to show that rates of amine attack upon ethyl chloroformate, methyl isothiocyanate and dimethylcarbamoyl chloride give linear correlations with n. Each of these reactions, involving nucleophilic attack at unsaturated carbon would also be expected to correlate with N_+, and thus Hall's observations are an indirect demonstration of a relationship between n and N_+. Interestingly, Hall reports s in the range 1.3–2.7 for these reactions at unsaturated carbon, consistent with the greater sensitivity to amine nucleophilicity that is demonstrated in eqns. (7)–(12) for the 1-methyl-4-vinylpyridinium cation relative to methyl 4-nitrobenzenesulfonate. The correlation[16] of rate constants for the aminolysis of ethylene oxide with N_+ implies a relationship between n and N_+ since these reactions are demonstrated in Table 4 to be also correlated with n. There has also been a recent demonstration[34] that nucleophilic attack upon triaryl cations may be described by n defined[3] for attack upon methyl iodide in methanol solution.

We hope that the availability of both n and N_+ parameters for a wide range of amine nucleophiles will encourage the further exploration of the interdependence of these two measures of nucleophilicity in a broad range of reactions. In particular, the systematic study of the reactivity of more hindered carbon electrophiles than methyl or methylene groups towards a variety of amines should provide considerable insight into the quantitative description of the role of steric phenomena in nucleophile–electrophile combination reactions.

Experimental

Methyl 4-nitrobenzenesulfonate (99%) was purchased from Aldrich. All amines were available from the accompanying study,[10] and amine buffer solutions were prepared as described in that work. All inorganic salts were ACS reagent-grade materials. The reactions of nucleophilic anions (with the exception of cyanide ion) were studied in solutions of total ionic strength 0.1 (KCl + nucleophile salt). Chloride ion was demonstrated to be a sufficiently weak nucleophile in these reactions that its reaction (at 0.1 mol dm^{-3}) with methyl 4-nitrobenzenesulfonate was not discernible to within experimental error above the background reaction due to water. Cyanide ion was studied in solutions of ionic strength 0.1 mol dm^{-3} (KCN + KOH), with correction of k_{obs} for the contribution from hydroxide ion nucleophile using the independently determined value of k_{Nu} for hydroxide ion (Table 2).

All rate data were obtained by monitoring the change in absorbance at 280 nm in aqueous solutions of ionic strength 0.1 mol dm^{-3} at 25 °C in a Perkin Elmer Lambda 2 spectrophotometer. All data collection and analysis followed the methods previously described.[10]

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References

1 C. D. Ritchie and P. O. I. Virtanen, *J. Am. Chem. Soc.*, 1972, **94**, 4966.
2 C. G. Swain and C. B. Scott, *J. Am. Chem. Soc.*, 1953, **75**, 141.
3 R. G. Pearson, H. Sobel and J. Songsted, *J. Am. Chem. Soc.*, 1968, **90**, 319.
4 J. F. Bunnett, *Ann. Rev. Phys. Chem.*, 1963, **14**, 271.
5 H. K. Hall, Jr., *J. Org. Chem.*, 1964, **29**, 3539.
6 J. Koskikallio, *Acta Chem. Scand.*, 1969, **23**, 1490.
7 M. J. Gregory and T. C. Bruice, *J. Am. Chem. Soc.*, 1967, **89**, 4400.
8 J. E. Dixon and T. C. Bruice, *J. Am. Chem. Soc.*, 1971, **93**, 6592.
9 B. L. Knier and W. P. Jencks, *J. Am. Chem. Soc.*, 1980, **102**, 6789.

10 C. K. M. Heo and J. W. Bunting, *J. Chem. Soc., Perkin Trans. 2*, 1994, preceding paper.

11 R. K. Burkhard, J. E. Lothers, Jr. and H. A. Smith, *Arch. Biochem. Biophys.*, 1959, **81**, 1.

12 R. E. Robertson, *Prog. Phys. Org. Chem.*, 1967, **4**, 213.

13 (*a*) D. D. Perrin, *Dissociation Constants of Organic Bases in Aqueous Solution*, Butterworth, London, 1965; *Supplement* 1972, Butterworth, London, 1972; (*b*) J. J. Christensen, R. M. Izatt, D. P. Wrathall and L. D. Hansen, *J. Chem. Soc. A*, 1969, 1212; (*c*) W. P. Jencks and J. Regenstein, *Handbook of Biochemistry*, The Chemical Rubber Co., Cleveland, 1968, pp. J150–J189; (*d*) J. W. Bunting and D. Stefanidis, *J. Am. Chem. Soc.*, 1990, **112**, 779.

14 T. S. Moore, D. B. Somervell and J. N. Derry, *J. Chem. Soc.*, 1912, **101**, 2459.

15 J. Hansson, 'The Reaction between Alkylene Oxides and Amines', *Lindstedt's Lund*, 1955, (*Chem. Abstr.*, 1958, **52**, 849).

16 P. O. I. Virtanen and R. Korhonen, *Acta Chem. Scand.*, 1973, **27**, 2650.

17 K. Okamoto, S. Fukui and H. Shingu, *Bull. Chem. Soc. Jpn.*, 1967, **40**, 1920.

18 G. C. Lalor and E. A. Moelwyn-Hughes, *J. Chem. Soc.*, 1965, 2201.

19 J. Koskikallio, *Acta Chem. Scand.*, 1969, **23**, 1477.

20 M. F. Hawthorne, G. S. Hammond and B. M. Graybill, *J. Am. Chem. Soc.*, 1955, **77**, 486.

21 P. R. Wells, *Chem. Rev.*, 1963, **63**, 171.

22 J. M. W. Scott, *Can. J. Chem.*, 1970, **48**, 3807.

23 A. B. Ash, P. Blumbergs, C. L. Stevens, H. O. Michel, B. E. Hackley, Jr. and J. Epstein, *J. Org. Chem.*, 1969, **34**, 4070.

24 J. Koskikallio, *Acta Chem. Scand.*, 1972, **26**, 1201.

25 S. Jokinen, E. Luukkonen, J. Ruostesuo, J. Virtanen and J. Koskikallio, *Acta Chem. Scand.*, 1971, **25**, 3367.

26 J. O. Edwards, *J. Am. Chem. Soc.*, 1956, **78**, 1819.

27 J. O. Edwards and R. G. Pearson, *J. Am. Chem. Soc.*, 1962, **84**, 16.

28 R. G. Pearson and J. Songstad, *J. Am. Chem. Soc.*, 1967, **89**, 1827.

29 P. Dietze and W. P. Jencks, *J. Am. Chem. Soc.*, 1989, **111**, 5880.

30 P. Dietze and W. P. Jencks, *J. Am. Chem. Soc.*, 1986, **108**, 4549.

31 S. Osterman-Golkar, L. Ehrenberg and C. A. Wachtmeister, *Radiation Botany*, 1970, **10**, 303.

32 Y. Kawazoe, S. Ninomiya, K. Kohda and H. Kimoto, *Tetrahedron Lett.*, 1986, **27**, 2897.

33 C. D. Ritchie, *J. Am. Chem. Soc.*, 1975, **97**, 1170.

34 N. J. Pienta and R. J. Kessler, *J. Am. Chem. Soc.*, 1993, **115**, 8330.

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